GIS 1

PHARMACOLOGY

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Doctor:

This sheet is based on the first online lecture which is only 20 minutes so it's going to be a short one :)

First, we're going to talk about the innervation and hormonal control of the GI track:

1- **Neuronal control**: As we know from the physiology course, there are two intramural plexuses in the GIT:

✓ The Myenteric plexus (Auerbach's plexus)
✓ The submucous plexus (Meissner's plexus)
✓ They're interconnected
✓ They constitute the ENS, which receives innervations from the 2 parts of the ANS:
  - Parasympathetic: by preganglionic fibres of the Vagus nerve.
  - Sympathetic: by postganglionic fibers releasing NE
  - Remember: some sympathetic cholinergic neurons, which have alpha 2 receptors, and their stimulation by NE, will inhibit the secretion of NE presynaptically(negative feedback).
✓ The neurons within the plexuses secrete Ach, NE, serotonin, purines, NO & pharmacological active peptides.
✓ The ENS also contain sensory neurons which respond to mechanical and chemical stimuli, so when the food stretches the walls of the stomach, for example, it will trigger a certain effect (neural reflex) that will cause evacuation of its content.

2- **Hormonal control**:
  ✓ The endocrine secretions are mainly peptides synthesized by the endocrine cells in the mucosa such as Gastrin & cholecystokinin.
  ✓ The paracrine secretions include many regulatory peptides released from special cells in the GIT, the most important example is Histamine, which is secreted by enterochromaffin-like cells in the stomach.

Now let's talk about the **Gastric secretions**:

- The stomach secretes 2.5 litres of gastric juice daily.
- The principal exocrine components are Prorennin and Pepsinogen secreted by the chief cells, HCl and intrinsic factor secreted by the parietal cells.

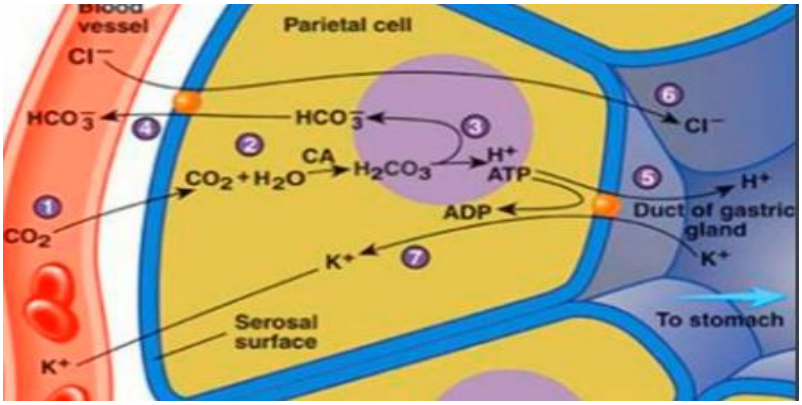
*HCl is important for promoting proteolytic digestion of foodstuffs, iron absorption and killing pathogens.

- Mucus-secreting cells also exist in large numbers in the gastric mucosa. Bicarbonate ions are secreted and trapped in the mucus, creating a gel-like protective barrier that maintains the mucosal surface at a pH of 6–7 in the face of a much more acidic environment (pH 1–2) in the lumen, so it protects the stomach from HCl & pepsin.
- Alcohol and bile can disrupt this protective layer. Locally produced prostaglandins stimulate the secretion of both mucus and bicarbonate. Disturbances in these secretory and protective mechanisms with Aspirin for example are involved in the pathogenesis of peptic ulcer, and gastro-oesophageal reflux disease (GORD or GERD) and injury caused by nonsteroidal anti-inflammatory drugs (NSAIDs).
- For the digestive enzyme pepsin to work the stomach must be at low pH (1.8-3.5) which is maintained by the secretion of about 2.5 litres of HCl daily by Parietal cells.

HCl secretion:

1- The stimulation of acid secretion involves the translocation of the H+/K+-ATPase to the apical membrane, which is a pump that pumps H+ into the lumen of the gland in exchange for K+ ions.
2- carbonic anhydrase catalyses the combination of CO2 and water to give carbonic acid, which dissociates into H+ and HCO3- inside the cell.
3- HCO3- exchanges Cl- from the blood at the basal membrane of the cell, then Cl- is pumped into the lumen.

*for more clarification about this mechanism refer to the Physiology secretions handout.



Regulation of acid secretion:

Stimulants:

- ✓ Ach from enteric neurons.
- ✓ Histamine from ECL (enterochromaffin - like) cells.
- ✓ Gastrin released by G cells.

MOA:

G cells release Gastrin → Gastrin binds the CCK2 receptors on ECL cells → ECL cells release Histamine → Histamine acts on H2 receptors on parietal cells to elevate cAMP → activation of proton secretion.

Direct vagal stimulation (parasympathetic) can also provoke acid secretion through a release of Ach which directly stimulates M1 receptors on parietal cells.

Inhibitors:

- ✓ Somatostatin released by D cells
- ✓ Prostaglandins

MOA:

Gastric pH < 3 → gastric D cells release Somatostatin → inhibition of acid secretion by 2 ways:

1- Directly by its effect on parietal cells
2- Indirectly by inhibiting release of Histamine & Gastrin.

Somatostatin exerts a tonic inhibitory influence on G cells, ECL and parietal cells.

local prostaglandins exert inhibitory effects predominantly on ECL cell function.

Phases of gastric acid secretion:

- ✓ **Cephalic Phase**:
  Any sight, smell, taste or thought of food, activate enteric neurons via the vagus nerve.
  In humans, the major effect of gastrin is indirect through the release of histamine from ECL cells not through direct parietal cell stimulation.

- ✓ **Gastric Phase**:
  Food stretch stomach walls activating a neural reflex to stimulate acid secretion.
  Peptides & amino acids stimulate G cells to release gastrin.
  Food acts as a buffer, raising the pH & thus removing the stimulus of somatostatin secretion until it's fully digested.
- ✓ **Intestinal Phase**: Once chyme enters the duodenum; it activates negative feedback mechanisms to reduce acid secretion.

Now let's talk about uses of drugs that inhibit or neutralise gastric acid secretion:

The principle clinical indications that require such effect are:

- ✓ Peptic ulcers: duodenal or gastric
- ✓ Gastro-oesophageal reflux disease (GORD): in which gastric secretion causes damage to the oesophagus (if untreated can cause dysplasia of the epithelium which may progress to a potentially dangerous pre-cancerous condition called Barret's oesophagus)
- ✓ Zollinger-Ellison syndrome: rare hypersecretory condition caused by gastrin-producing tumour.

Peptic ulcer:

A defect in the lining of the stomach or the duodenum.

Causes:

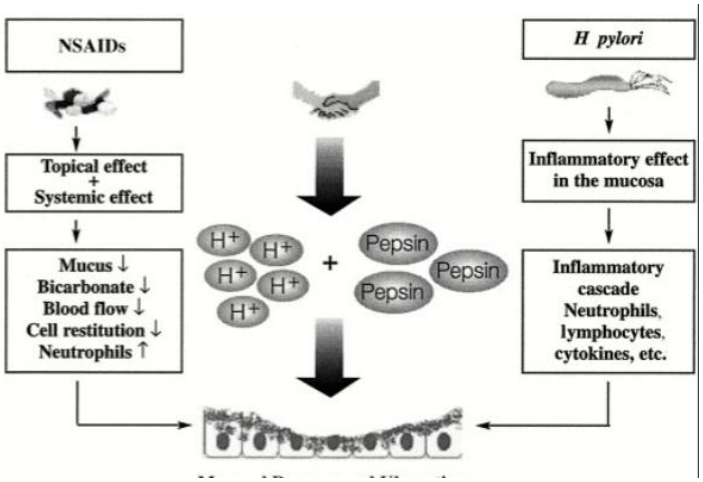
The causes of peptic ulcers are not fully understood, although infection of the stomach mucosa with Helicobacter pylori -most common- causes chronic gastritis, now considered to be a major cause (especially of duodenal ulcer).

Many NSAIDs (like aspirin) cause gastric bleeding and erosions by inhibiting cyclo-oxygenase-1, the enzyme responsible for synthesis of protective prostaglandins. (recall that they're inhibitors of HCl secretion)

Other factors: Smoking, Stress, alcohol, Gastrinomas such as Zollinger Ellison syndrome

as we can see here, NSAIDs decrease mucus, Bicarbonate, & blood flow ,thus, damaging the protective membrane.

H.Pylori causes an inflammatory cascade, which damages the mucosa as well.



Symptoms:

burning pain in stomach between meals and at night, bloating, heartburn, nausea or vomiting.

In severe cases, symptoms include: Dark or black stool (due to bleeding), Vomiting blood (hematemesis), Weight loss & severe pain in the mid to upper abdomen.

Complications:

- ✓ GI bleeding: sudden and large bleeding can be life threatening
- ✓ Cancer: H.Pylori as the etiological factor
- ✓ Perforation (hole in the wall) Penetration.

Treatment options:

- ✓ Reduce acid secretion by Proton pump inhibitors or H2 antagonists or neutralize it in the lumen by antacids.
  ***** they used to use Atropine in the past but it's not very effective and it has to be given in high doses.
- ✓ Protect the mucosa
- ✓ Antibiotics to eradicate the bacteria (H.pylori)

If it this is successful, then the ulcer should begin to heal by its own.

The next sheet will be talking about the drugs, stay home and good luck!